REMARKS

Amendments to the Specification

Applicants have amended the abstract to improve its form and to refer to "[m]ethods for isolating a plurality of cells encoding a plurality of different RNAs associated with a same nucleic acid tag sequence, comprising the step of exposing the cells to a same signaling probe that produces a detectable signal upon hybridization to the same nucleic acid tag sequence." Support for this amendment may be found, *inter alia*, in claim 19.

Applicants have also amended the specification to note that it is the national stage of an international application, and to delete embedded hyperlinks. Further, applicants have amended the specification to improve its form.

No new matter is added by these amendments. Their entry is respectfully requested.

Amendments to the Claims

Applicants have added new claim 145. Support for new claim 145 may be found, *inter alia*, in paragraph [0018] of the specification as originally filed.

Applicants have amended claim 114 to refer to a library suitable for use in a cell-based screening assay. Support for this amendment may be found, *inter alia*, in paragraphs [0154]-[0157] of the specification as originally filed.

Applicants have amended claim 120 to refer to a plurality of RNAs "selected from the group consisting of RNAs in the same or a related biological pathway, RNAs that act upstream or downstream of each other, RNAs that have a modulating, activating or repressing function to each other, RNAs that are dependent on each other for function or activity, RNAs that are components of the same complex, and RNAs that encode proteins selected from the

group consisting of proteins in the same or a related biological pathway, proteins that act upstream or downstream of each other, proteins that have a modulating, activating or repressing function to each other, proteins that are dependent on each other for function or activity, proteins that are components of the same complex, and proteins from the same protein family." Support for this amendment may be found, *inter alia*, in former claim 120.

Applicants have rewritten claim 121 as an independent claim.

Applicants have amended claim 127 to replace the expression "lethal or damaging to the cell" with the expression "damaging to the cell."

Applicants have amended claims 129 and 143 to replace the expression "preselected RNA" with the expression "second RNA, wherein said second DNA sequence is under the control of a conditional promoter." Support for these amendments may be found, *inter alia*, in paragraph [0013] of the specification as originally filed.

Applicants have amended claim 130 to refer to the steps of (1) assaying the isolated cells for the presence of the second RNA, and (2) identifying the test RNA that activates the conditional promoter in cells that express the second RNA. Support for this amendment may be found, *inter alia*, in paragraph [0013] of the specification as originally filed.

Applicants have amended withdrawn claim 131 to depend from claim 129, and to replace the expression "tissue specific" with the expression "conditional." Support for this amendment may be found, *inter alia*, in paragraph [0013] of the specification as originally filed.

Finally, applicants have amended claims 19, 25, 121, 127, 131, 132, and 144 to improve their form.

Applicants expressly reserve the right to pursue any canceled or deleted subject matter in subsequent applications that claim benefit from this application.

None of the above amendments adds new matter. Their entry is respectfully requested. Upon entry of the amendments, claims 19, 21, 25, 34, 46, 49, 50, 103, 109, 110, 114, and 117-145 will be pending in this application, with claims 46, 49, 50, 103, 109, 110, 114, 128, and 131-144 having been withdrawn from initial consideration.

Abstract

The Examiner has objected to the Abstract as allegedly failing to comply with the requirements of 37 C.F.R. § 1.72(b).

Applicants have amended the Abstract to improve its form and to refer to "[m]ethods for isolating a plurality of cells encoding a plurality of different RNAs associated with a same nucleic acid tag sequence, comprising the step of exposing the cells to a same signaling probe that produces a detectable signal upon hybridization to the same nucleic acid tag sequence." Applicants believe that the Abstract as amended complies with the requirements of 37 C.F.R. § 1.72(b).

Specification

The Examiner has objected to the specification, contending that "the first line of the specification does not contain the PCT information" (Office Action, p. 5). Applicants have amended the specification to refer to International Patent Application No. PCT/US2005/005080, of which the subject application is a national stage entry, thereby obviating this objection.

Further, the Examiner has objected to the specification for containing "an embedded hyperlink and/or other form of browser-executable code" (Office Action, p. 5). Applicants have amended the specification to delete hyperlinks, thereby obviating this objection.

Rejections under 35 U.S.C. § 112 -- Indefiniteness

Claims 120 and 127 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite for lacking antecedent basis for the expression "the proteins encoded."

Applicants have amended claim 120 to refer to "RNAs that encode proteins," thereby providing antecedent basis for the proteins referenced in the claim. Further, applicants have amended claim 127 to replace the expression "the protein encoded by the RNA" with the expression "a protein encoded by the RNA." Applicants' amendments obviate this rejection.

Claim 121 stands rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite. According to the Examiner, it appears that the method steps recited in claim 121 are replacing the method steps recited in claim 19, instead of incorporating all of the steps of claim 19. Applicants have rewritten claim 121 as an independent claim, as suggested by the Examiner, thereby obviating this rejection.

Claim 125 stands rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite for being an "improper use claim" under MPEP § 2173.05(q) (Office Action, p. 7).

Applicants disagree. According to MPEP § 2173.05(q), "[a]ttempts to claim a process without setting forth any steps involved in the process generally raises an issue of indefiniteness under 35 U.S.C. 112, second paragraph." Claim 125, however, sets forth the steps involved in the claimed method. Claim 125 depends from and thus comprises the steps of claim 19, which are:

(1) introducing into cells a plurality of DNAs encoding a plurality of different RNAs, wherein each DNA further encodes a nucleic acid tag sequence, and wherein at least a subset of the plurality of DNAs encodes the same nucleic acid tag sequence;

(2) exposing the cells to a signaling probe that produces a detectable signal upon hybridization to said same nucleic acid tag sequence; and

(3) isolating the cells that produce the signal.

Claim 125 further comprises the step of "selecting the cells using the selection marker after introducing the DNA into the cells but prior to exposing said cells to the signaling probe." Accordingly, claim 125 clearly indicates the steps of the claimed method as required by MPEP § 2173.05(q), and is not indefinite.

Claim 127 stands rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite as directed to a cell expressing a lethal product. Without conceding the correctness of this rejection, but merely to expedite prosecution, applicants have amended claim 127 to refer to a method "wherein the RNA encoded by the DNA, or a protein encoded by the RNA, is damaging to the cell when expressed." Applicants' amendments obviate this rejection.

Rejections under 35 U.S.C. § 102 -- Anticipation

Claims 19, 21, 25, 34, 117-127, 129, and 130 stand rejected under 35 U.S.C. § 102(a) as allegedly anticipated by U.S. Patent No. 6,692,965 ("Shekdar"). According to the Examiner:

> . . . Shekdar et al. teach methods comprising introducing into cells at least one DNA encoding at least one antisense RNA or mRNA (i.e. protein encoding; expression) and at least one epitope tag (i.e. encompassing library, first and second library, etc.), exposing the cells to molecular beacons that hybridize to the antisense RNA, mRNA, and/or nucleic acid encoding the epitope tag(s), isolating cells that fluoresce, and culturing cells to produce cell lines wherein cells can be pooled or mixed wherein the epitope tag can be in frame or out of frame with the DNA encoding the RNA, selection markers can be utilized, promoters are utilized, and the RNA or protein encoded by the RNA can be lethal to the cells. . . Regarding the functional limitations (i.e. "preselected", "test", "same or related biological pathway", "upstream or downstream of each other", "modulating, activating, or repressing function to each other", "dependent on each other for function or activity", "components of the same complex", or "same protein family"), applicants are respectfully directed to MPEP § 2173.05(g). (Office Action, p. 8.

Further, claims 19, 21, 25, 117-120, 122-127, 129, and 130 stand rejected under 35 U.S.C. § 102(e) as allegedly anticipated by U.S. Patent Publication No. 2003/0215798 ("Short"). According to the Examiner:

> . . . Short et al. teach methods of identifying and isolating clones comprising introducing expression libraries into cells and utilizing molecular beacons to detect cells wherein selection markers, promoters, etc. may be utilized. (Office Action, pp. 8-9.)

Applicants traverse.

The subject application is the first disclosure of a method of isolating a plurality of cells comprising the steps of:

(1) introducing into cells a plurality of DNAs encoding a plurality of different RNAs, wherein each DNA further encodes a nucleic acid tag sequence, and wherein at least a subset of the plurality of DNAs encodes the same nucleic acid tag sequence;

(2) exposing the cells to a signaling probe that produces a detectable signal upon hybridization to said same nucleic acid tag sequence; and

(3) isolating the cells that produce the signal.

Shekdar does not refer to such a method. To anticipate, Shekdar must disclose each and every limitation of the rejected claims. It does not. For example, Shekdar does not recite a method of isolating a plurality of cells encoding a plurality of different RNAs associated with a same nucleic acid tag sequence. Accordingly, claims 19, 21, 25, 34, 117-127, 129, and 130 are not anticipated by Shekdar.

The case is even stronger in regard to Short. Short in fact relates to a fundamentally different invention than the present invention. Short refers to a high throughput functional screen using FACS sorting to identify cells in a prokaryotic expression library that possess a biological activity of interest, i.e., an enzymatic activity. Variations of this core

method include enrichment steps, e.g., by use of molecular beacons concurrently with enzymatic substrates that fluoresce during the FACS sorting process. However, this does not change the fact that Short is sorting for positive clones based on enzymatic activity. In contrast, the present invention relates to methods of isolating living cells based on RNA detection. Accordingly, claims 19, 21, 25, 117-120, 122-127, 129, and 130 are not anticipated by Short.

For the above reasons, applicants respectfully request reconsideration and withdrawal of these rejections.

Nonstatutory Obviousness-Type Double Patenting Rejection

Claims 19, 21, 25, 34, 117-127, 129, and 130 stand rejected on the ground of nonstatutory obviousness-type double patenting as allegedly obvious over claims 1-33 of Shekdar. Further, claims 19, 21, 25, 34, 117-127, 129 and 130 stand provisionally rejected on the ground of nonstatutory obviousness-type double patenting as allegedly obvious over claims 1-43 of copending U.S. Patent Application No. 12/771,223 ("the '223 application").

With regard to the double patenting rejection over Shekdar, applicants note that, pursuant to 37 C.F.R. § 1.130(a), a timely filed terminal disclaimer in compliance with 37 C.F.R. § 1.321(c) may be used to overcome a double patenting rejection. Applicants stand ready to submit a terminal disclaimer over Shekdar upon indication of otherwise allowable subject matter.

With regard to the provisional double patenting rejection over the '223 application, applicants stand ready to respond to the rejection or to provide a terminal disclaimer, as appropriate, upon allowance of the claims of the '223 application if the instant claims are still subject to an obviousness-type double patenting rejection in view of those allowed claims.

CONCLUSION

Applicants request favorable consideration of the application as amended and early allowance of the pending claims. To that end, the Examiner is invited to telephone the undersigned to discuss any issue pertaining to this reply.

Respectfully submitted,

/WYAN-CHING M. LEE/

Jane T. Gunnison (Reg. No. 38,479)
Attorney for Applicants
Wyan-Ching M. Lee (Reg. No. 65,813)
Agent for Applicants
ROPES & GRAY LLP
Customer No. 81098